PB88-178744

# Health and Environmental Effects Profile for 2-Nitropropane

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Cincinnati, OH

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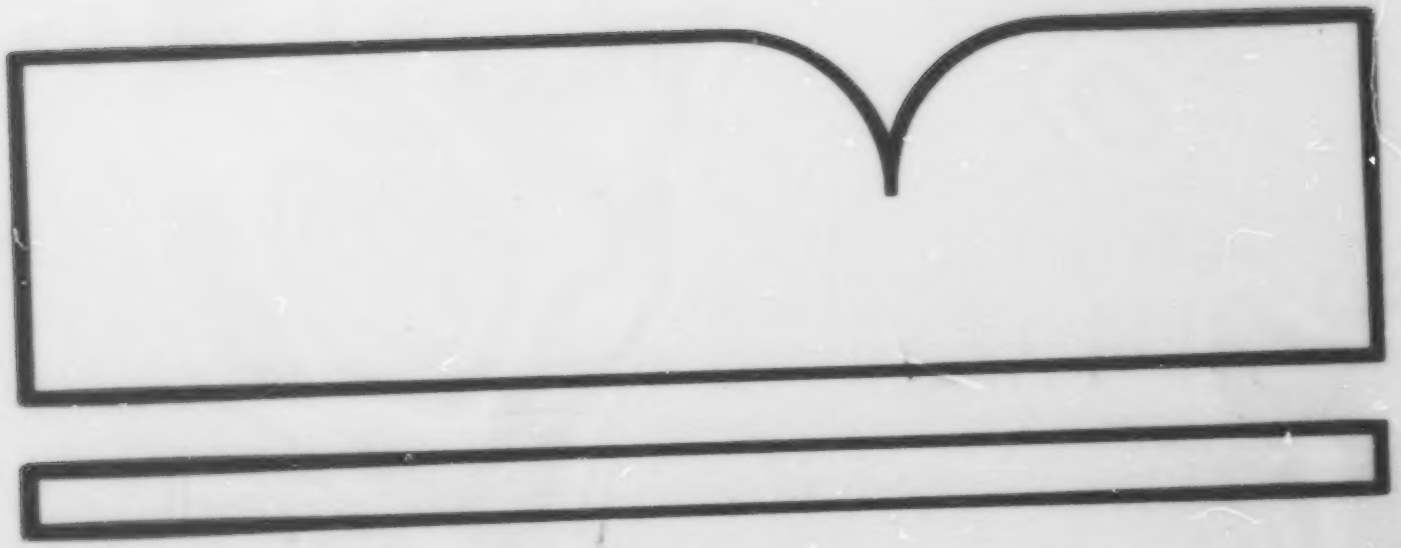

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# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2-NITROPROPANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for 2-nitropropane was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 2-Nitropropane has been evaluated as a carcinogen. The human carcinogen potency factor ($q_1^*$) for 2-nitropropane is 9.36 (mg/kg/day)-1 for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 2-nitropropane is 1000.

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## PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of $q_1^*$ (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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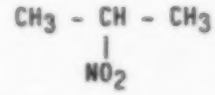
## LIST OF ABBREVIATIONS

| | |
|---|---|
| BCF | Bioconcentration factor |
| bw | Body weight |
| CS | Composite score |
| i.p. | Intraperitoneal |
| i.v. | Intravenous |
| $LC_{50}$ | Concentration lethal to 50% of recipients |
| $LD_{50}$ | Dose lethal to 50% of recipients |
| MED | Minimum effective dose |
| ppm | Parts per million |
| RQ | Reportable Quantity |
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| s.c. | Subcutaneous |
| SGT | Serum glutamic transaminase |
| STEL | Short-term exposure limit |
| TWA | Time-weighted average |
| UV | Ultraviolet |
| v/v | volume per volume |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

2-Nitropropane is the common chemical name, but this compound is also known by the synonyms 2-NP, NiPar S-20 and nitroisopropane. The structure for 2-nitropropane is as follows:



The molecular weight for 2-nitropropane is 89.095 and the empirical formula is $C_3H_7NO_2$. The Chemical Abstract Service (CAS) Registry number is 79-46-9.

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Nitropropane is a colorless liquid with a mild odor. Selected physical properties are listed below and are taken from Baker and Bollmeier (1981) unless otherwise noted.

| | | |
|---|---|---|
| Melting point: | -91.32°C | |
| Boiling point: | 120.25°C | |
| Density: | 0.988 g/cm³ at 20°C | |
| Refractive index: | 1.39439 at 20°C | |
| Vapor pressure: | | |
| 20°C | 13.0 mm Hg | |
| 25°C | 18.0 mm Hg | |
| Vapor density (air = 1.0): | 3.06 | |
| Flash point (open cup): | 37.8°C | |
| Ionization constant: | $7.7 \times 10^{-9}$ ($K_{acl}$)<br>2.1x10-8 (Knitro) | |
| Air-Water partition coefficient: | 0.005 | (Hansch and Leo, 1981) |
| Water solubility: | 17,000 ppm at 25°C | |

2-Nitropropane is miscible with organic solvents including aromatic hydrocarbons, alcohols, esters, ketones, ethers and carboxylic acids.

2-Nitropropane can be condensed with a variety of aldehydes and ketones to yield nitroalcohols (Baker and Bollmeier, 1981). In the presence of alkali it undergoes chlorination and can be reduced to the amine by various reducing agents. It is resistant to oxidation, and prolonged heating results in decomposition.

## 1.3. PRODUCTION DATA

2-Nitropropane is produced commercially, in conjunction with nitromethane, nitroethane and 1-nitropropane, by reacting nitric acid with excess propane (Baker and Bollmeier, 1981). SRI (1984) currently lists ANGUS Chemical Co. in Sterlington, LA and the W.R. Grace Co. in Deer Park, TX as manufacturers.

Current production figures for 2-nitropropane are not available. For 1977, Finklea (1977) estimated that production of 2-nitropropane was 30 million pounds, of which 18 million pounds were either used captively or exported and 12 million pounds were sold in the United States.

## 1.4. USE

Nearly all of the 2-nitropropane sold in the United States is used as a solvent for products such as coatings, inks and adhesives (IARC, 1982). It is also used as a processing solvent to separate closely related materials in natural products or in reaction mixtures and as a medium for chemical reactions (Baker and Bollmeier, 1981).

2-Nitropropane is used commercially as an intermediate in the synthesis of nitroalcohols and alkanolamines (Baker and Bollmeier, 1981). It has minor uses in explosives, propellants and fuels (racing cars).

## 2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

### 2.1. WATER

The fate of 2-nitropropane in water will depend upon its ability to undergo chemical, photochemical and biological reactions and partitioning (transport) from the water column into air or sediment. Chemical studies concerning the hydrolysis of 2-nitropropane in aqueous solution were not located in the available literature. The chemical structure of 2-nitropropane indicates that significant hydrolysis is not likely to occur under environmental conditions.

The UV spectrum, as determined in a cyclohexane solvent, shows that 2-nitropropane has an absorption maximum at 278 nm, with significant absorption in the environmentally relevant range of >290 nm (Sadtler, 1961). This indicates that photolysis is likely to occur, although the rate of photodecomposition can only be determined experimentally. Data regarding photolysis rates in aqueous media were not located in the available literature. Irradiation of 5.0 g of 2-nitropropane in 200 mL cyclohexane for 30 hours gave 0.21 g propan-2-ol, 0.26 g nitrocyclohexane, 0.77 g N-cyclohexylacetamide, 0.80 g N-cyclohexyl-N-methylacetamide and 1.30 g N-isopropylcaprolactam in addition to small amounts of the solvent oxidation products, cyclohexanone and cyclohexanol (Reid et al., 1974).

Data regarding the microbial degradation of 2-nitropropane in aqueous media were not located in the available literature. Data presented in Section 2.3. indicate that various cell-free extracts from selected microbes are able to chemically alter 2-nitropropane. The significance of microbial degradation in the water environment is not clear.

The transport of 2-nitropropane in the aquatic environment will depend on the ability of the compound to volatilize, to absorb to particulate

organic matter or to bioaccumulate in aquatic organisms. Specific experimental data for these transport mechanisms were not available; however, estimations can be generated using the physical properties of 2-nitropropane. The water solubility and vapor pressure of 2-nitropropane can be used to calculate the water-to-air ($K_w$) partition ratio from the following equation (Swann et al., 1983):

$$K_w = \frac{(0.0624)\ (\text{water solubility in ppm})\ (\text{Temp., °K})}{(\text{vapor pressure in mm Hg})\ (\text{molecular weight in g/mol})}$$

Using the water solubility (17,000 ppm) and vapor pressure (18 mm Hg) data at 25°C from Section 1.2., the calculated $K_w$ value for 2-nitropropane is ~200. Therefore, at equilibrium, ~0.5% of the 2-nitropropane present will be in the air phase. The $K_w$ value is basically the inverse of Henry's Law constant.

The soil absorption coefficient ($K_{oc}$) and the BCF can be estimated from the following equations (Kenaga, 1980):

$\log K_{OC} = 3.64 - 0.55(\log WS) \pm 1.23$ orders of magnitude (95% confidence limit)

$\log BCF = 2.791 - 0.564(\log WS) \pm 1.99$ orders of magn'tude (95% confidence limit)

where WS is the water solubility in ppm. For 2-nitropropane, the $K_{oc}$ and BCF values, based on water solubility, are ~20 and 2.5, respectively. These values indicate that 2-nitropropane is very mobile in soil and unlikely to bioaccumulate. Therefore, in the aquatic enviroment, 2-nitropropane is not likely to be transported from the water to particulate matter or to aquatic organisms in significant amounts.

## 2.2. AIR

Chemicals present in the atmosphere can be removed by either chemical or physical processes. The chemical removal processes include reaction with

.hydroxyl radicals, reaction with ozone, reaction with other radicals, or photolytic transformations. The physical removal processes include dissolution, adsorption on aerosol particles and dry deposition (Cupitt, 1980). Cupitt (1980) has theoretically calculated the gas-phase rate constant for the initial reaction between hydroxyl radicals and 2-nitropropane to be $55 \times 10^{12}$ $cm^3$/mol-sec and has estimated that photolysis is possible. From this rate constant, Cupitt (1980) calculated that 2-nitropropane present in the atmosphere will be reduced to 36.9% of its original value in 0.2 days, with formaldehyde and acetaldehyde as the anticipated products. Cupitt (1980) further estimates that physical processes are unlikely to remove 2-nitropropane from the air.

Levy (1973) reported the photochemical smog reactivity of 2-nitropropane to be relatively low. The basic technique for measuring this reactivity is to irradiate a mixture of the organic compound of interest (2-nitropropane), nitric oxide and air in a smog chamber using a light source that simulates natural sunlight. In a comparative study of 45 commercial solvents, Levy (1973) found that under the laboratory conditions of 4 ppm organic solvent and 2 ppm nitric oxide the photochemical-smog production potential of 2-nitropropane was low. These results indicate that 2-nitropropane, in combination with nitric oxide in the atmosphere, can undergo chemical alteration.

## 2.3. SOIL

Although few studies have been reported concerning the fate and transport of 2-nitropropane in soil, several studies have been conducted on its biodegradation. Dhawale and Hornemann (1979) found that crude cell-free extracts of nine strains of Streptomyces were able to produce nitrous acid

from 2-nitropropane. The oxidative denitrification of these extracts with 2-nitropropane was characterized by the following reaction:

$$2CH_3CH(NO_2)CH_3 + O_2 \rightarrow 2CH_3COCH_3 + 2HNO_2$$

In addition, Hansenula mrakii was similarly able to oxidize 2-nitropropane. Patel et al. (1982) found that methane monooxygenase produced by the facultative methane-utilizing organism, Methylobacterium sp. (CRL-26), as isolated and enriched from soil samples, was able to oxidize 2-nitropropane. Kido et al. (1975) tested 14 strains of bacteria, fungi and yeasts for their ability to grow in a medium of 0.2% peptone, 0.2% glycerol and 2-nitropropane. 2-Nitropropane inhibited the growth of all strains except Sarcina lutea, Brevibacterium protophormiae, Hansenula mrakii and Rhizopus batatas. Enzyme preparations derived from Hansenula mrakii were able to oxidatively decompose 2-nitropropane to yield nitrite. Kido et al. (1975) suggested that Hansenula mrakii and its enzyme (and other microorganisms able to utilize nitro compounds) could be used to decompose nitro compounds found in industrial waste water. The significance of the microbial degradation of 2-nitropropane in the natural environment, however, is not clear.

The photolysis of 2-nitropropane from soil surfaces has not been investigated. As noted in Section 2.1., the UV spectra for 2-nitropropane shows considerable absorption in the environmentally significant range of >290 nm. Paszyc (1971) has reported that liquid 2-nitropropane at 25°C is photolyzed to compounds that include methyl cyanide, water, propane, $NO_2$, $(CH)_2CO$, isopropyl alcohol and isopropyl-ONO; photolysis rates were not given. It is, therefore, possible that the photodegradation of 2-nitropropane from soil surfaces may have some environmental significance.

As noted in Section 2.1., the soil adsorption coefficient ($K_{oc}$) for 2-nitropropane can be calculated to be ~20 using the equation reported by

Kenaga (1980). This value would indicate that 2-nitropropane is not tightly bound to the organic matter in soil and is, therefore, easily leached. Experimental adsorption data were not available.

The relatively high vapor pressure of 2-nitropropane, 18.0 mm Hg at 25°C, suggests that it would rapidly evaporate from dry soil surfaces. Under this condition, volatilization would likely be the predominant environmental fate mechanism. In wet soils, this result is not as clear because of the high water solubility (17,000 ppm) of 2-nitropropane.

## 3. EXPOSURE

### 3.1. WATER

Pertinent data regarding environmental exposure to 2-nitropropane in water were not located in the available literature as cited in Appendix A. The U.S. EPA STORET Data Base reports no listing for 2-nitropropane.

### 3.2. FOOD

Pertinent data regarding exposure to 2-nitropropane in food were not located in the available literature as cited in Appendix A.

### 3.3. INHALATION

2-Nitropropane has been detected in the air of a rubber tire manufacturing plant at a concentration of <0.2 mg/m³ [0.05 ppm] (NIOSH, 1978). Nitroparaffin workers exposed to 2-nitropropane in a chemical plant had a daily exposure of ~3.65 mg/m³ [1 ppm] (NIOSH, 1977).

Hoffman and Rathkamp (1968) detected 0.73 µg of 2-nitropropane in the smoke from one filterless, 85 mm United States blend cigarette, which correlated with nitrate contents of the tobacco.

### 3.4. DERMAL

Pertinent data regarding dermal exposure to 2-nitropropane were not located in the available literature as cited in Appendix A.

## 4. PHARMACOKINETICS

### 4.1. ABSORPTION

Nolan et al. (1982) exposed male rats by inhalation to 2-nitro-[1,3-$^{14}$C]propane at levels of either 154 (5.5 hours) or 20 (6 hours) ppm. Immediately following exposure, levels of radioactivity in the blood were either 3.6 (20 ppm exposure) or 33.3 (154 ppm exp.) µg eq./g, while levels of unchanged 2-nitropropane were either 0.6 (20 ppm exposure) or 7.1 (154 ppm exposure) µg/mL, indicating that most of the radioactivity was associated with metabolites.

Similar results were obtained by Müller et al. (1983) when male rats confined to a chamber were exposed to 200 ppm 2-nitropropane in air for 3 hours. Unchanged 2-nitropropane (3 µg/mL) and its metabolites, acetone (30 µg/mL) and isopropanol (0.66 µg/mL), were detected in the plasma immediately following exposure.

Blood samples taken after 10 minutes from rats injected i.p. with either 25 or 50 mg 2-nitropropane/kg contained unchanged 2-nitropropane (20.3±1.7 or 16.9±13.5 µg/mL), acetone (7.5±1.2 or 10.4±1.3 µg/mL), and isopropanol (0.41±0.2 or 0.31±0.2 µg/mL), respectively (Müller et al., 1983).

### 4.2. DISTRIBUTION

Rats exposed by inhalation to either 20 or 154 ppm 2-nitro[1,3-$^{14}$C]-propane (see Section 4.1.) retained 26 and 11%, respectively, of the administered radioactivity in the tissues and carcass 48 hours after exposure. The highest concentrations of radioactivity were found in the kidneys, lungs and liver. Less than 5% of the radioactivity in the liver was incorporated into hepatic macromolecules. After 48 hours, the radioactivity in the tissues decreased 2- to 5-fold (Nolan et al., 1982).

Müller et al. (1983) injected rats i.p. with $^{14}$C-2-nitropropane and observed that 2-nitropropane and its metabolites are initially deposited in the fat and then redistributed into other tissues (Table 4-1).

4.3. METABOLISM

In rats and chimpanzees, 2-nitropropane is readily metabolized to acetone, isopropanol and unspecified polar metabolites (Müller et al., 1983). After exposure by inhalation to 200 ppm 2-nitropropane, male rats had initially high plasma levels of unchanged 2-nitropropane (3 µg/mℓ immediately following exposure), which then declined over a 3-hour period (1.0 µg/mℓ at T=3 hours). Immediately following exposure. plasma levels of acetone (30 µg/mℓ plasma) and isopropanol (0.43-0.66 µg/mℓ plasma) were also high and remained high throughout the 3-hour analysis period. Similar trends were noted in male rats following i.p. injection of 2-nitropropane (see Section 4.1.), except that levels of acetone and isopropanol reached peak values after 120-360 minutes post-treatment.

Urine collected from chimpanzees 6-24 hours after i.v. injection with $^{14}$C-2-nitropropane (10 mg/kg) contained acetone (3.1 µg/mℓ), isopropanol (7.2 µg/mℓ), and 2-nitropropane (1.8 µg/mℓ). At 24 hours postadministration, unspecified polar metabolites accounted for 90% of the urinary radioactivity. A similar pattern of urinary metabolite formation was observed in rats injected i.p. with 2-nitropropane; preliminary analysis indicated that rats and chimpanzees may form different urinary conjugates with the 2-nitropropane metabolites (Müller et al., 1983).

Also, evidence indicates that 2-nitropropane is metabolized by mammalian microsomes isolated from liver. Ullrich and Schnabel (1973) and Mansuy et al. (1977) demonstrated that 2-nitropropane can bind with cytochrome P450 in microsomes derived from rats and rabbits. Ullrich et al. (1978) and Sakurai

TABLE 4-1

Distribution of Radioactivity Expressed as µg 2-NP/g of Tissue
in Rats After Intraperitoneal Injection with $^{14}C$-2-NP (50 mg/kg bw)*

| Organ/Tissue | 1 Hour | 40 Hours | 8 Days |
|---|---|---|---|
| Lungs | 7.0 | 12.9 | 5.6 |
| Liver | 8.2 | 15.3 | 8.0 |
| Kidney | 8.6 | 15.5 | 6.8 |
| Adrenal | 3.4 | 20.6 | 23.1 |
| Bone marrow | 1.9 | 26.7 | 6.4 |
| Brain | 4.2 | 6.3 | 3.0 |
| Blood | 9.9 | 3.3 | 3.3 |
| Muscle | 6.2 | 2.2 | 2.4 |
| Testes | 7.9 | 6.4 | 3.3 |
| Spleen | 6.5 | 13.7 | 5.3 |
| Bone | 0.8 | 7.5 | 1.3 |
| Fat: s.c. | 14.3 | 2.6 | 3.5 |
| peripheral | 14.5 | 4.2 | 2.9 |
| omental | 13.1 | 10.0 | 2.1 |

*Source: Müller et al., 1983

et al. (1980) further demonstrated that 2-nitropropane is denitrified in the presence of microsomes from rat liver, NADPH and oxygen to form acetone and nitrite.

Ivanevitch et al. (1978) demonstrated that 2-nitropropane can actually degrade the heme moiety of cytochrome P450 *in vitro*. These authors contend that metabolites formed by cytochrome P450 are directly responsible for the degradation, and that this mechanism may act to protect the cell from damage by trapping reactive metabolites.

4.4. ELIMINATION

Rats exposed by inhalation to 2-nitro[1,3-$^{14}$C]propane (either 154 ppm for 5.5 hours or 20 ppm for 6 hours) eliminated ~50% of the administered radioactivity from the lungs as $^{14}CO_2$ (both doses), and either 3.7% (20 ppm) or 21.9% (154 ppm) from the lungs as unchanged 2-nitropropane within 48 hours of administration (Nolan et al., 1982). Radioactivity was also eliminated from the urine (8%, 20 ppm; 11%, 154 ppm) and feces (11%, 20 ppm; 5%, 154 ppm) within 48 hours of administration. Elimination of radioactivity from the blood was biphasic ($T_{0.5}$=71 minutes and 13.2 hours, 154 ppm; $T_{0.5}$=64 mintues and 16.4 hours, 20 ppm), while elimination of unchanged 2-nitropropane from the blood was linear ($T_{0.5}$=48 minutes). Pulmonary elimination of unchanged 2-nitropropane was biphasic, with $T_{0.5}$=172 minutes and 36 hours for an exposure of 154 ppm and $T_{0.5}$=364 minutes and 36 hours for an exposure of 20 ppm.

Rats injected i.p. with $^{14}$C-2-nitropropane (50 mg/kg) eliminated 53% of the administered radioactivity from the lungs (4.5% as 2-nitropropane, 10.4% as acetone, and 38.1% as $CO_2$), 0.7% in the feces and 5.9% in the urine 40 hours after treatment (Müller et al., 1983).

Chimpanzees injected i.v. with $^{14}$C-2-nitropropane (10 mg/kg) eliminated most of the administered radioactivity from the lungs (percent not specified), and small amounts in the urine (5.5-5.7%) and feces (0.42-0.47%) (Müller et al., 1983). Elimination of radioactivity from the plasma was biphasic, with $T_{0.5}$=5.5 hours and 48 hours.

## 5. EFFECTS

### 5.1. CARCINOGENICITY

Finklea (1977) and IARC (1982) reviewed a chronic inhalation study conducted by Lewis et al. (1979). In this study, Sprague-Dawley rats (50 males/group) and New Zealand white rabbits (15 males/group) were exposed by inhalation to either 0, 27 or 207 ppm 2-nitropropane (0, 98+11 or 754+55 mg/m³, respectively, 94.5% pure by weight, 3.1% 1-nitropropane, 2% nitroethane, 0.4% 2-nitro-2-methylpropane), for 7 hours/day, 5 days/week. Ten rats/group were killed and examined after 2 days, 10 days, 1 month, 3 months and 6 months of exposure. Five rabbits/group were killed and examined after 1, 3 and 6 months. "Basophilic foci of hyperplastic small hepatocytes" were observed in 4/9 rats exposed to 207 ppm (754 mg/m³) for 3 months. At 6 months, all 10 rats exposed to 207 ppm (754 mg/m³) had multiple hepatocellular carcinoma. No other compound-related tumors were observed in any other animals. Finklea (1977) noted that since food and water were present during exposure, 2-nitropropane may have been ingested as well as inhaled.

In another study, Griffin et al. (1980, 1981) exposed groups of 125 male and 125 female Sprague-Dawley rats to 0 or 25 ppm (91 mg/m³) 2-nitropropane (96.65% pure, 3.63% 1-NP, 0.2% nitroethane, 0.51% 2-nitromethylpropane) for 7 hours/day, 5 days/week, for 22 months. Groups of 10 males and 10 females were killed and examined after 1, 3, 6 and 12 months of exposure. All remaining rats were killed and examined after 22 months. No compound-related tumors were observed; however, 3/250 controls and 13/249 exposed animals had focal areas of hepatocellular nodules.

Griffin et al. (1978a,b) and Griffin and Coulston (1983) also reported results of similarly designed studies, in which the rats were exposed to either 100 or 200 ppm of 2-nitropropane. The animals exposed to 100 ppm

were terminated at 18 months. No effects were observed in the female rats. In the male rats, absolute liver weight was increased from 16 g in the control to 52 g in the treated animals. In addition, the incidence of hepatic masses and nodules was 22/23 in the treated rats compared with 0/62 in the controls. Hepatic masses were first observed at interim kills at 9 months after the start of exposure. Similar increases in liver weights were reported in male rats exposed at 200 ppm in the interim 6-month report of this study (Griffin et al., 1978b). At the 6-month sacrifice 5/10 animals had developed hyperplastic areas or nodules. Hyperplastic changes were not observed in females, although mild signs of hepatotoxicity were apparent. A final report on the animals exposed to 200 ppm of 2-nitropropane was not available.

Miller et al. (1979) conducted an epidemiology study for International Minerals and Chemical Corporation, the sole manufacturer in 1975 of 2-nitropropane. The cohort consisted of workers considered by job description to be directly exposed to 2-nitropropane (372 workers), indirectly exposed (366 workers) or to have no exposure. During the study period, limited monitoring data indicated that 2-nitropropane levels were generally <25 ppm, although excursions of up to 1640 ppm occurred at times. More extensive monitoring after 1977 suggested that TWA levels of between 0.2 and 10 ppm were most common. For males, there was no increase in the incidence of cancers at all sites, nor in the incidence of hepatic cancers. In females, there was an increase in deaths from cancers at all sites; however, only two females were in the group directly or indirectly exposed to 2-nitropropane and these cancers were not considered exposure-related. There was also a relatively high incidence of sarcomas; however, again, these tumors were not associated with exposure and occurred in different organs, suggesting that

the etiology was not the same. When the data were analyzed in relation to latency period or exposure period, there were no trends indicating increased risk.

IARC (1982) has concluded that there is sufficient evidence for the carcinogenicity of 2-nitropropane in animals, but that evidence regarding the carcinogenicity of 2-nitropropane to humans is inadequate. Applying the IARC criteria for evaluating the overall weight of evidence, 2-nitropropane would be classified as Group 2 chemical (i.e., "probably" carcinogenic to humans).

## 5.2. MUTAGENICITY

Lofroth et al. (1981) examined the mutagenicity of 2-nitropropane in strains TA98, TA100 and TA1535 of Salmonella typhimurium. A positive response was observed (doses not reported) both in the presence and absence of S-9. Similar results were obtained in strains TA98 and TA100 at doses up to 20 mg/plate (Speck et al., 1982), and in strains TA1537, TA92, TA98 and TA100 at doses of up to 0.1 mL 2-nitropropane/plate (Hite and Skeggs, 1979).

Negative results were obtained with 2-nitropropane in the micronucleus test (Hite and Skeggs, 1979). In this test, CD-1 mice were orally exposed to 0.1, 0.2 or 0.3 mL 2-nitropropane/kg/day for 2 days. Erythrocytes were examined when bone marrow was extracted from mice killed 6 hours after the last dose.

## 5.3. TERATOGENICITY

Groups of 10-15 female Sprague-Dawley rats were injected i.p. with 2-nitropropane (170 mg/kg in corn oil) on days 1-15 of gestation (Hardin et al., 1981; Harris et al., 1979). Pregnancy was confirmed by the presence of sperm in the vagina. On the 21st day of gestation, dams were killed and their uterine contents and internal organs were examined both grossly and

microscopically. Fetuses were weighed, measured and examined for external, skeletal and soft-tissue malformations. Fetotoxic, but not teratogenic, effects were observed in pups taken from mothers injected with 2-nitropropane. Development of the heart was delayed by 1-2 days in pups from 9/10 litters (30-86% of pups affected in a given litter). A chart in the paper by Hardin et al. (1981) indicated that 2-nitropropane-treated dams yielded fetuses with reduced pre- or post- implantational survival and reduced body weight or length in comparison with controls; details, however, were not reported. No maternal toxicity was observed.

## 5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of 2-nitropropane were discussed in Section 5.3. of this report.

## 5.5. CHRONIC TOXICITY

IARC (1982) and Finklea (1977) reviewed a chronic inhalation study conducted by Lewis et al. (1979) on Sprague-Dawley rats and New Zealand white rabbits (see Section 5.1.). Animals were exposed to 0, 27 or 207 ppm (0, 98, 754 mg/m³, respectively) 2-nitropropane for 7 hours/day, 5 days/week, for 6 months. No compound-related effects were observed in rabbits exposed to any level of 2-nitropropane or in rats exposed to 27 ppm 2-nitropropane. Rats exposed to 207 ppm 2-nitropropane, however, had mild pulmonary edema and hemorrhagic foci in the lungs, elevated levels of serum glutamic-pyruvic transaminase, increased liver weights and a greater incidence of necrotic foci and hypertrophic areas in the liver (with distorted architecture of acini) in comparison with controls.

In another chronic inhalation study, Griffin et al. (1980, 1981) (reviewed by IARC, 1982) exposed Sprague-Dawley rats to 25 ppm (91 mg/m³) 2-nitropropane for 7 hours/day, 5 days/week for 22 months (see Section

5.1.). There were no compound-related effects on body weight, organ weights, clinical chemistry variables or hematology (including methemoglobin formation), and no indication of an increase in levels of nitrite. Males, but not females, had a slight increase in focal vacuolization of the cytoplasm of hepatocytes in comparison with controls. The compound-related increase in focal areas of hepatocellular nodules was discussed in Section 5.1. of this profile.

At higher exposures (the same protocol as above) Griffin et al. (1978a,b) and Griffin and Coulston (1983) observed signs of hepatotoxicity in male rats. In male rats exposed to 100 ppm 2-nitropropane for 18 months, both relative and absolute liver weight was increased, SGT was elevated and body weight was depressed. These changes were observed initially at the 9- and 12-month interim sacrifice. Effects were not observed in females at this exposure level. At exposures of 200 ppm, Griffin et al. (1978a,b) described in an interim 6-month report similar toxic changes in the liver of male animals. In comparison with male rats, only mild signs of hepatotoxicity were apparent in female rats.

IARC (1982) and Finklea (1977) reviewed inhalation studies conducted by Treon and Dutra (1952) on several species of animals. Rats, guinea pigs and rabbits (two animals of each species/treatment) survived 130 seven-hour exposures to 328 ppm (1197 mg/m$^3$) 2-nitropropane. No histological changes were reported by Treon and Dutra (1952), but a reexamination of the liver sections taken from the rats (Finklea, 1977) indicated the presence of foci similar to those seen in the study by Lewis et al. (1979) in rats exposed to 207 ppm 2-nitropropane. Methemoglobinemia and Heinz body formation were observed in rabbits but not in rats or guinea pigs. Cats exposed in a sim-

ilar manner to 328 ppm 2-nitropropane died within 17 days of exposure. Methemoglobinemia, Heinz body formation, severe liver damage and pulmonary edema and hemorrhage were observed in these cats.

IARC (1982) and Finklea (1977) reviewed a study by Skinner (1947). Continuous occupational exposure to 20-45 ppm (73-164 mg/m³) 2-nitropropane caused vomiting, diarrhea, anorexia and severe headaches in six workers, who recovered completely overnight. The severity of these symptoms increased during damp weather. Two workers exposed intermittently to 10-30 ppm (36-108 mg/m³) suffered no ill-effects.

## 5.6. OTHER RELEVANT INFORMATION

Four cases of fatal poisoning from acute exposure to 2-nitropropane or 2-NP-containing products were reviewed by Hine et al. (1978). In all cases, men were using the product in a confined area with poor ventilation. Mean survival time for these individuals was 6-10 days. Autopsies revealed severe kidney and liver damage. No solvent was detected in the blood and methemoglobin formation was not observed.

Male rats injected i.p. with 50 mg 2-nitropropane/kg bw had liver damage (centrilobular necrosis, degranulation of rough endoplasmic reticulum, proliferation of smooth endoplasmic reticulum, mitochondrial abnormalities, elevated serum alanine aminotransferase) and reduced levels of acetylcholinesterase activity in the brain within 24 hours of administration (Zitting et al., 1981) (Table 5-1).

TABLE 5-1

Acute Toxicity of 2-Nitropropane*

| Route | Species | Value |
|---|---|---|
| Inhalation | rat | $LC_{50}$ = 400 ppm (6 hour exposure) |
| Intraperitoneal | mouse | $LD_{50}$ = 75 mg/kg |

*Source: RTECS

## 6. AQUATIC TOXICITY

### 6.1. ACUTE

Curtis and Ward (1981) attempted to determine the acute 96-hour $LC_{50}$ of 2-nitropropane in the fathead minnow, Pimephales promelas, and found no mortality at 612.5 ppm, the highest concentration tested.

Pertinent data regarding chronic toxicity to aquatic life, effects on plants or residue levels of 2-nitropropane were not located in the available literature as cited in Appendix A.

## 7. EXISTING GUIDELINES AND STANDARDS

The Occupational Safety and Health Administration standard for occupational exposure to 2-nitropropane is a TWA of 25 ppm (90 mg/m³) (Code of Federal Regulations, 1981). The ACGIH (1983) has also adopted a TWA of 25 ppm (90 mg/m³), but has announced an intended change to a TWA of 10 ppm (35 mg/m³) with an STEL of 20 ppm (70 mg/m³) on the basis of suspected carcinogenic potential.

Adhesives intended for use in the transport or packaging of food are permitted to contain 2-nitropropane (Code of Federal Regulations, 1982).

Amoore and Hautala (1983) reported an air odor threshold of $70 \pm 2.2$ ppm (v/v) for 2-nitropropane.

## 8. RISK ASSESSMENT

Chronic inhalation exposure to ≥25 ppm 2-nitropropane caused toxic effects in cats, rats, guinea pigs and rabbits (Treon and Dutra, 1952; Lewis et al., 1979; Griffin et al., 1980, 1981). Occupational exposure to 2-nitropropane (20-45 ppm) resulted in vomiting, diarrhea, anorexia and severe headaches in male workers (Skinner, 1947). Intraperitoneal injection of 170 mg 2-nitropropane/kg during days 1-15 of gestation caused fetotoxicity but not maternal toxicity or teratogenic effects in rats (Harris et al., 1979; Hardin et al., 1981).

Multiple hepatocellular carcinomas were observed in 10/10 male Sprague-Dawley rats that were exposed by inhalation to 207 ppm (754 mg/m³) 2-nitropropane for 7 hours/day, 5 days/week for 6 months (Lewis et al., 1979). No tumors were observed in controls or rats exposed to 27 ppm 2-nitropropane. In another inhalation study, no compound-related tumors were observed in Sprague-Dawley rats (male and female) exposed to 25 ppm (91 mg/m³) 2-nitropropane for 7 hours/day, 5 days/week for 22 months (Griffin et al., 1980, 1981). There was, however, an increase in the incidence of focal areas of hepatocellular nodules in 2-nitropropane-treated rats in comparison with controls. Epidemiological evidence of the carcinogenicity of 2-nitropropane to humans is of limited value because of the limited numbers of chronically exposed individuals (NIOSH, 1980, reviewed by IARC, 1982).

Based on these studies, IARC (1982) has concluded that there is sufficient evidence for the carcinogenicity of 2-nitropropane in animals and would be a Group 2 chemical (i.e., "probably carcinogenic to humans). It is, therefore, appropriate to derive a $q_1^*$ for 2-nitropropane. Using the data of Lewis et al. (1979), the linearized multistage model (Federal Register, 1980) yields a $q_1^*$ of $2.429 \times 10^{-2}$ $(mg/kg/day)^{-1}$ for rats (see

Appendix B for details). To derive a $q_1^*$ for humans, the animal $q_1^*$ is multiplied by the cube root of the body weight ratio, $(70/0.35)^{1/3}$, which has been demonstrated empirically to adjust for species-to-species extrapolation, and a value that accounts for less-than-lifetime exposure, $(730/180)^3$ (Federal Register, 1980). This yields a $q_1^*$ of 9.36 $(mg/kg/day)^{-1}$.

## 9. REPORTABLE QUANTITY RANKING BASED ON CHRONIC TOXICITY

Pertinent chronic toxicity data and concomitant CSs are summarized in Table 9-1. To obtain human doses in mg/day, exposures of mg/m³ were transformed by the following equation:

$$\underset{(\text{mg/day})}{\text{dose}} = \underset{(\text{mg/m}^3)}{C} \times \underset{(\text{hour/day})}{E} \times \underset{(\text{days/week})}{D} \times \underset{(\text{inhalation rate})}{I}$$

where I = .224 m³/day.

The highest CS of 13.8 was obtained from the study by Griffin et al. (1981) in rats. An $RV_e$ of 6 was assigned on the basis of pronounced pathological changes in the liver (Table 9-1), and an $RV_d$ of 2.3 was derived from the log MED. Multiplying the $RV_e$ and the $RV_d$ yields a CS of 13.8, associated with an RQ for 2-nitropropane of 1000 (Table 9-2).

The Treon and Dutra (1952) study also included cats, which were exposed to 2-nitropropane at 1197 mg/m³; all cats died within 17 days of initial treatment. Since mortality in cats was an acute effect in this study, it is inappropriate to calculate a CS for mortality in cats. Although a CS can be derived for the other species in this study that survived the 6 months of exposure with effects associated with an $RV_d$ of 5, the early mortality of the cats at the same exposure level makes the CS derived from this study difficult to interpret.

TABLE 9-1

RQs for the Chronic Inhalation Toxicity of 2-Nitropropane

| Species | Animal Exposure | Human MED (mg/day) | $RV_d$ | Effects | $RV_e$ | CS | RQ | Reference |
|---|---|---|---|---|---|---|---|---|
| Rat | 754 mg/m³, 7 hours/day, 5 days/week for 6 months | 1204 | 1 | pulmonary edema and hemorrhagic foci in the lungs; liver damage (necrotic foci and hypertrophic areas in liver, elevated SGT, increased weight); hepatocellular carcinoma in 10/10 rats examined at 6 months* | 9 | 9 | 1000 | Lewis et al., 1979 |
| Rat | 91 mg/m³, 7 hours/day, 5 days/week for 22 months | 145 | 2.3 | increase in focal areas of hepatocellular nodules (13/249 exposed vs. 3/250 controls); focal vacuolization of hepatocytes (males only) | 6 | 13.8 | 1000 | Griffin et al., 1980, 1981 |
| Rats, guinea pigs, rabbits | 1197 mg/m³, 7 hours/exposure for 130 exposures (6 months) | 2678 | 1 | rats; necrotic foci in liver; methemoglobinemia and Heinz body formation in rabbits | 5 | 5 | 5000 | Treon and Dutra, 1952 |

*Information on neoplastic effects is included for the sake of completeness. $RV_e$ values are based on non-neoplastic effects.

TABLE 9-2

2-Nitropropane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

| | |
|---|---|
| Route: | inhalation |
| Dose*: | 145 mg/day |
| Effect: | increase in focal areas of hepatocellular nodules, focal vacuolization of hepatocytes in males |
| Reference: | Griffin et al., 1980, 1981 |
| $RV_d$: | 2.3 |
| $RV_e$: | 6 |
| Composite Score: | 13.8 |
| RQ: | 1000 |

*Equivalent Human Dose

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## APPENDIX A

## LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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## APPENDIX B

### Cancer Data Sheet for Derivation of $q_1^*$

Compound: 2-nitropropane

Reference: Lewis et al., 1979

Species, Strain, Sex: rat/Sprague-Dawley/male

Body Weight: 0.35 kg (assumed)

Length of Exposure ($l_e$) = 180 days

Length of Experiment ($L_e$) = 180 days

Lifespan of Animal (L) = 730 days

| Experimental Doses or Exposures, 7 hours/day, 5 days/week | Transformed Dose mg/kg/day | Incidence No. Responding/No. Tested (or Examined) |
|---|---|---|
| 0 | 0 | 0/10 |
| 27 ppm (98 mg/m³) | 6.51 | 0/10 |
| 207 ppm (754 mg/m³) | 50.07* | 10/10* |

*Since multistage fails to converge with a "perfect response," an incidence of 9/10 and a dose of 45.06 (which is 9/10 of 50.07) were actually used to obtain a value for $q_1^*$.

$q_1^*$ Animal = $2.429 \times 10^{-2}$ $(mg/kg/day)^{-1}$

$q_1^*$ Human = $q_1^*$ Animal x $(730/180)^3$ x $(70/0.35)^{1/3}$

= 9.36 $(mg/kg/day)^{-1}$